

**REMARKS**

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Attached hereto is an Appendix showing the changes made to claims 1, 3-6, 8, and 9, as amended.

The rejection of claims 1-10 and 25 under 35 U.S.C. § 112 (2<sup>nd</sup> para.) is respectfully submitted in view of the above amendments removing the phrase "active fragments thereof" from the claims so that they only recite chemokines. However, applicants submit that such fragments are encompassed by the term "chemokine" to the extent those fragments function as chemokines.

The rejection of claims 1-10 and 25 under 35 U.S.C. § 112 (1<sup>st</sup> para.) for lack of enablement is respectfully traversed in view of the above amendments, deleting the phrase "active fragments thereof" and defining the term "binding domains" as "an antibody".

The rejection of claims 1-25 and 32-38 under 35 U.S.C. § 112 (2<sup>nd</sup> para.) for indefiniteness is respectfully traversed in view of the above amendments calling for "an antibody" instead of a "binding domain".

The rejections of claims 1-4 and of claims 1-8, 10, and 25 under 35 U.S.C. § 103 for obviousness over U.S. Patent No. 5,824,782 to Holzer et. al., ("Holzer") in view of Huston, et. al., "Protein Engineering of Single-Chain Fv Analogs and Fusion Proteins," Methods Enzymology 203: 46-88 (1991) ("Huston") is respectfully traversed.

Holzer discloses immunoconjugates which comprise a monoclonal antibody or fragment thereof, which is specific for the human EGF-receptor molecule, and a member of the chemokine family. The member of the chemokine family is preferably selected from C-X-C family, such IL-8. The immunoconjugates induce cytotoxic and chemotactic activity and are suitable for a targeted tumor therapy. Holzer's immunoconjugate binds the N-terminus of IL-8 to the carboxy terminus of the Fab fragment of the monoclonal antibody. Thus, Holzer does not satisfy the requirement of the claimed invention that the chemokine be "coupled to the N-terminus of the heavy or light chain of the antibody".

The portion of Huston relied on in the outstanding office action relates to the protein engineering of single-chain Fv analogs and fusion proteins. In these constructs, the single-chain Fv analogs are variable region fragments of antibodies which consist of a heavy-

chain variable region domain  $V_H$  non-covalently associated with a light-chain variable domain  $V_L$  in the form of a single chain. As explained on page 47, this single-chain Fv analog is prepared by connecting the genes encoding the  $V_H$  domain and the  $V_L$  domain with an oligonucleotide and recombinantly producing the  $V_H$  and  $V_L$  domains with a linker peptide connecting them. Thus, as noted in following passage on page 51, the single-chain Fv analog of Huston is distinguishable from the claimed antibody:

The single-chain Fv consists of a single polypeptide chain with the sequence  $V_H$ -linker- $V_L$  or  $V_L$ -linker- $V_H$ , as opposed to the classical Fv heterodimer of  $V_H$  and  $V_L$ .

Moreover, native IgG antibodies not only contain  $V_H$  and  $V_L$  domains but also constant regions  $C_H1$ ,  $C_H2$ , and  $C_H3$ , with all of these components arranged with respect to one another in the particular fashion shown in Figure 1A on page 49 of Huston. The single-chain Fv analogs of Huston not only lack the constant regions of IgG but also the native conformation of such antibodies. Since Huston does not utilize antibodies, it is clearly distinguishable from the claimed invention.

One of ordinary skill in the art would have no basis to adapt the teachings of Huston regarding single-chain Fv analogs to the immunoconjugates of Holzer. As noted above, the N-terminus of Holzer's IL-8 is bound to the monoclonal antibody. The rationale for this arrangement is set forth in column 7, lines 41-44 as follows:

It was demonstrated previously that the N-terminal portion of the IL-8 molecule with the highly conserved E-L-R-motif is required for receptor binding and signal transduction.

Figure 3 of Huston shows that the single-chain Fv can be fused at its amino- or carboxy-terminus to an effector. However, one of ordinary skill in the art would not adapt this teaching in Huston to Holzer, because it would undermine Holzer's expressed command that the entity attached to the antibody be bound at its N-terminus.

It is also improper to combine the teachings of Holzer and Huston with regard to the claimed invention, because the claims of the present application (and the disclosure of Holzer) call for an antibody as opposed to a single-chain Fv molecule. There is nothing in

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NOT  
in Claims

the references to indicate that single-chain Fv molecules have anything to do with antibodies or that teachings relating to the former can be applied to the latter.

A single-chain Fv molecule does not function in the same manner as an antibody. As noted above, the single-chain Fv analog of Huston lacks constant heavy chains  $C_{H1}$ ,  $C_{H2}$ , and  $C_{H3}$ . In particular,  $C_{H2}$  is the IgG domain which is important for complement activation (Tao, et. al., "The Differential Ability of Human IgG1 and IgG4 to Activate Complement is Determined by the COOH-terminal Sequence of the  $C_{H2}$  Domain," J. Exp. Med. 173: 1025-28 (1991) at page 1025 (attached hereto at Exhibit 1)) and critical for determining IgG receptor affinity (Canfield, et. al., "The Binding Affinity of Human IgG for its High Affinity Fc Receptor is Determined by Multiple Amino Acids in the  $C_{H2}$  Domain and is Modulated by the Hinge Region," J. Exp. Med. 173: 1483-91 (1991) at page 1483 (attached hereto at Exhibit 2)).  $C_{H3}$  must be present for maximal binding to the Fc $\gamma$  receptor. Id. at page 1486. The  $C_{H1}$  domain has the role in IgG association with the high affinity receptor of maintaining overall quaternary structure. Id. at page 1489. These functions of constant heavy chains  $C_{H1}$ ,  $C_{H2}$ , and  $C_{H3}$  are clearly important in the recruitment and stimulation of an antitumor immune response. Since Huston's single-chain Fv analog lacks these constant heavy chains and, as a result, the functions they achieve, one of ordinary skill in the art would not apply that reference's teachings to systems where antibodies are to be utilized (e.g., Holzer or the present invention).

For all of these reasons, the rejection based on the combination of Holzer and Huston should be withdrawn.

The rejection of claims 1 and 9 under 35 U.S.C. § 103 for obviousness over Huston in view of U.S. Patent No. 5,514,554 to Bacus ("Bacus") and Holzer is respectfully traversed. Bacus is cited as teaching monoclonal antibodies to her2/neu and does not overcome the above-noted deficiencies of Holzer and Huston. Accordingly, the rejection based on the combination of Huston, Bacus, and Huston should be withdrawn.

In view of all the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

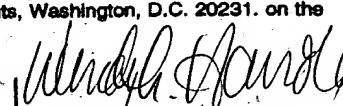
Respectfully submitted,

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## APPENDIX

The changes made by the amendments to claims 1, 3-6, 8, and 9 are shown below with insertions being underlined and deletions being bracketed.

1. (Twice Amended) A chimeric molecule suitable for stimulating a tumor specific immune response comprising:  
an antibody [binding domain] having heavy and light chains each with an N terminus and being capable of specifically binding to a tumor cell associated antigen, and  
a chemokine [or active fragment thereof], which is coupled to the N terminus of the heavy or light chain of the antibody [binding domain] such that the antibody [binding domain] remains capable of binding to the tumor cell associated antigen and the chemokine retains activity.
3. (Amended) The chimeric molecule according to claim [2] 1 wherein the chemokine [or active fragment thereof] is linked to the amino terminus of the [heavy or] light chain of the antibody.
4. (Amended) The chimeric molecule according to claim [3] 1, wherein the chemokine [or active fragment thereof] is linked to the amino terminus of the heavy chain of the antibody.
5. (Amended) The chimeric molecule according to claim 1, further comprising:  
a flexible linker or hinge region connecting the chemokine and the [binding domain] antibody.
6. (Twice Amended) The chimeric molecule according to claim 1, wherein the chemokine is selected from the group consisting of DC-CK1, SDF-1, fractalkine, lymphotactin, IP-10, Mig, MCAF, MIP-1 $\alpha$ , MIP-1 $\beta$ , IL-8, NAP-2, PF-4, and RANTES [and active fragments thereof].
8. (Amended) The chimeric molecule according to claim 1, wherein the antibody [binding domain] specifically binds to a tumor cell associated antigen from tumor

cells selected from the group consisting of breast cancer cells, ovarian cancer cells, lung cancer cells, bladder cancer cells, and prostate cancer cells.

9. (Amended) The chimeric molecule according to claim 1, wherein the antibody [binding domain] specifically binds to her2/neu.